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# Validation of Bleeding Risk Criteria (ARC-HBR) in Patients Undergoing Percutaneous Coronary Intervention and Comparison with Contemporary Bleeding Risk Scores

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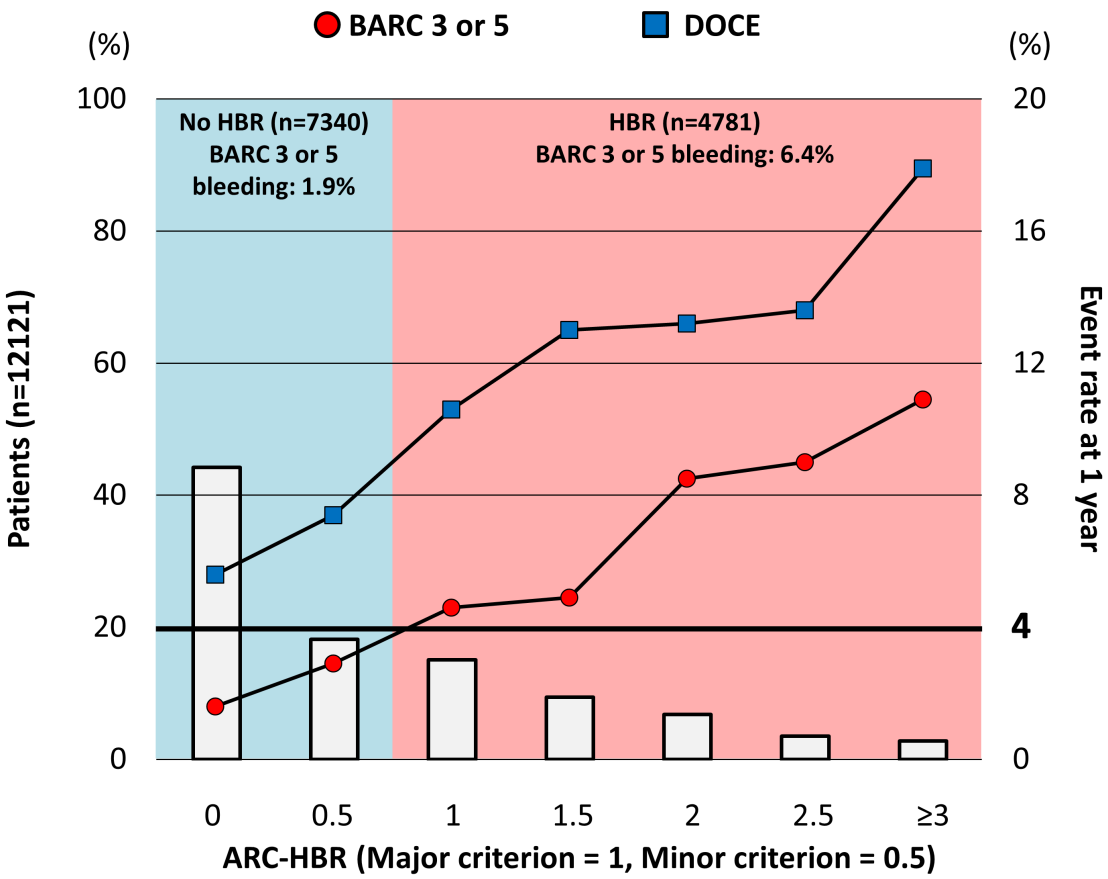
**Abstract**

**Aims:** The Academic Research Consortium for high bleeding risk (ARC-HBR) defined consensus-based criteria for patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI). We aimed to validate the ARC-HBR criteria for the bleeding outcomes using a large cohort of patients undergoing PCI.

**Methods and Results:** Between 2009 and 2016, patients undergoing PCI were prospectively included in the Bern PCI Registry. Patients were considered to be at HBR if at least 1 major criterion or 2 minor criteria were met. The primary endpoint was Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding at 1 year; ischemic outcomes were assessed using the device-oriented composite endpoints (DOCE) of cardiac death, target-vessel myocardial infarction, and target lesion revascularization. Among 12,121 patients, those at HBR (n=4,781, 39.4%) had an increased risk of BARC 3 or 5 bleeding (6.4% vs. 1.9%; P<0.001) and DOCE (12.5% vs. 6.1%; P<0.001) compared with those without HBR. The degree of risk and prognostic value was related to the risk factors composing the criteria. The ARC-HBR criteria had higher sensitivity than PRECISE-DAPT score and PARIS bleeding risk score (63.8%, 53.1%, 31.9%), but lower specificity (62.7%, 71.3%, 86.5%) for BARC 3 or 5 bleeding.

**Conclusion:** Patients at HBR defined by the ARC-HBR criteria had a higher risk of BARC 3 or 5 bleeding as well as DOCE. The bleeding risk was related to its individual components.

The ARC-HBR criteria was more sensitive to identify patients with future bleedings than other contemporary risk scores at the cost of specificity.



**Classifications:** ACS/NSTE-ACS, bleeding, coronary artery disease, stable angina

## Condensed abstract

We aimed to validate the ARC-HBR criteria for the bleeding outcomes in patients undergoing percutaneous coronary intervention. Patients were considered to be at high-bleeding risk (HBR) if at least 1 major criterion or 2 minor criteria were met. Among 12,121 patients, those at HBR (n=4,781, 39.4%) had an increased risk of BARC 3 or 5 bleeding (6.4% vs. 1.9%; P<0.001) and device-oriented composite endpoints (12.5% vs. 6.1%; P<0.001) compared with those without HBR. Patients at HBR defined by the ARC-HBR criteria had a higher risk of BARC 3 or 5 bleeding as well as DOCE.

**Abbreviations:**

ARC-HBR = academic research consortium for high bleeding risk

BARC = bleeding academic research consortium

CCS = chronic coronary syndrome

CKD = chronic kidney disease

DAPT = dual antiplatelet therapy

DOCE = device oriented composite endpoints

eGFR = estimated glomerular filtration rate

HBR = high bleeding risk

ICH = intracranial hemorrhage

MI = myocardial infarction

NACE = net adverse composite endpoints

OAC = oral anticoagulant

PCI = percutaneous coronary interventions

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

## Introduction

Following percutaneous coronary intervention (PCI), the impact of major bleeding on prognosis is at least as pronounced as myocardial infarction.[1, 2] Dual antiplatelet therapy (DAPT) reduces the risk of stent and non-stent related ischemic adverse events in patients undergoing PCI; however, this benefit is offset at least in part in patients at high bleeding risk (HBR) and directly related to the duration of DAPT. A recent study demonstrated that patients at HBR did not yield benefit from long-term DAPT irrespective of the underlying ischemic risk, suggesting that the characterization of bleeding risk outweighs ischemic risk (i.e. PCI complexity) in terms of optimal DAPT duration.[3]

Although several bleeding prediction scores are currently available and received a Class IIb (Level A) recommendation in the 2017 European Society of Cardiology Focused Update on DAPT to characterize patients undergoing PCI,[4] they afford a modest discrimination ability with an average C statistics of approximately 0.7 to predict bleeding.[5, 6] In the clinical trial setting, heterogeneous definitons of HBR have been applied across numerous studies, which may limit the interpretation and generalizability of reported data.[7-9] Against this background, the Academic Research Consortium for High Bleeding Risk (ARC-HBR), a collaboration among leading research organizations, regulatory authorities, and physician-scientists from the United States, Asia, and Europe focusing on PCI–related bleeding, developed a consensus-based definition of patients at HBR in May 2019.[10] HBR was arbitrarily defined as 1-year risk

of ≥4% for a bleeding academic research consortium (BARC) 3 or 5 bleeding or ≥1% for intracranial hemorrhage (ICH). To date, data on the applicability of the ARC-HBR criteria in the real-world setting is scarce. Therefore, we validated the ARC-HBR criteria to predict bleeding outcomes using prospective data from a large cohort of unselected, consecutive patients undergoing PCI.

## Methods

*Patient population*

All consecutive patients undergoing PCI at Bern University Hospital, Switzerland, have been prospectively enrolled into the Bern PCI Registry (NCT02241291) between January 2009 and December 2016. For the present study, patients undergoing balloon angioplasty alone or implantation of bioresorbable scaffolds and those in whom ARC-HBR criteria could not be completely ascertained were excluded. The registry was approved by the institutional ethics committee. All patients provided written informed consent.



*ARC-HBR criteria*

Some of the ARC-HBR criteria needed to be modified or were not available due to the data availability in the registry, as summarized in **Supplementary table 1**. Major and minor ARC-HBR criteria applied in the current study are as follows: age ≥75 years (minor); oral

anticoagulant or novel oral anticoagulant at discharge (major), estimated glomerular filtration rate (eGFR) <30ml/min (major) and eGFR ≥30, <60 ml/min (minor); baseline hemoglobin <11 g/dL (major), and 11–12.9 g/dL for men and 11–11.9 g/dL for women (minor); spontaneous non-intracranial bleeding requiring hospitalization or transfusion (major); thrombocytes at index PCI <100 $\times 10^9$/L (major); NSAIDS at discharge (minor); cancer history within 1 year prior to index PCI and/or on-going treatment, excluding non-melanoma skin cancer (major); previous intracranial bleeding or previous stroke (major); any ischemic stroke at any time not meeting the major criterion (minor). Definitions of the ARC-HBR criteria are provided in the **Appendix.** Patients were considered to be at HBR if at least 1 major criterion or 2 minor criteria were met.[10] The ARC-HBR score was calculated by adding 1 point for any major criterion and 0.5 point for any minor criterion.



*Procedure*

PCI was performed according to current guidelines.[11] Heparin (at least 5000 IU or an initial bolus of 100 I.U. per kg body weight) was used for procedural anticoagulation with the aim to maintain an ACT >250msec. The periprocedural use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Dual antiplatelet therapy (DAPT) consisting of acetylsalicylic acid and a P2Y12 inhibitor was initiated before, at the time, or immediately after the procedure. Prasugrel was introduced as of September 2009, and ticagrelor as of November 2011. The

majority of patients with chronic coronary syndrome (CCS) received clopidogrel. The routinely recommended DAPT duration was 12 months.[12]

*Clinical endpoints*

The primary bleeding endpoint was bleeding defined as Bleeding Academic Research Consortium (BARC) 3 or 5.[13] Secondary endpoints, definitions, and patient follow-up are provided in the **Appendix**.

*Statistical analysis*

Continuous variables were summarized as mean ± standard deviation or median and interquartile ranges, and compared with Student's t test or the Mann-Whitney U test. Binary and categorical variables were calculated as frequencies (percentages), and were compared with the chi-square test or Fischer's exact test. Kaplan-Meier cumulative event curves were constructed for time-to-event variables and compared using the log-rank test. Subhazard ratio was obtained from a competing risk survival regression based on Fine and Gray's proportional subhazard model. Discrimination of the bleeding risk score was assessed by the C statistic. Calibration was assessed by comparing predicted probabilities with observed frequency of BARC 3 or 5 bleeding. Cox regression analysis was performed to test the prognostic significance of each component of the ARC-HBR criteria for BARC 3 or 5 bleeding and DOCE.

Each component of the ARC-HBR criteria was adjusted by all components of the ARC-HBR criteria and clinically important variables reported by previous studies. For BARC 3 or 5 bleeding, female, body mass index, current smoker, hypertension, peripheral artery disease, acute coronary syndrome, and potent P2Y12 at discharge; for DOCE, age, female, current smoker, hypertension, peripheral artery disease, previous myocardial infarction, previous revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), left ventricular ejection fraction, stent type (bare-metal stent, first-generation drug-eluting stent were entered into a multivariate model.[5, 6, 14, 15] P-values were 2-tailed and considered under 0.05 as statistically significant in all analyses. Statistical analyses were performed with R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).



**Results**

*Patients*

Of 13,748 patients enrolled into the Bern PCI Registry between January 2009 and December 2016, 12,121 patients were analyzed for the present study with complete follow-up available in 11314 (93.3%) patients at 1 year. Patients were excluded in case of balloon angioplasty without stent implantation (n=496), implantation of bioresorbable scaffolds (n=60), or if not all of the ARC-HBR criteria were assessable (n=1071: missing hemoglobin [n=437], missing eGFR [n=710], missing thrombocytes [n=564], missing data on NSAIDs [n=152]).

*Baseline characteristics*

Clinical and procedural characteristics and medication status are summarized in **Table 1 and Supplementary tables 2 and 3**. Patients at HBR (n=4781, 39.4%) were older and more commonly female, had more risk factors for atherosclerotic cardiovascular disease, comorbidities, CCS as an indication for PCI, and had higher PRECISE-DAPT scores compared with those without. Among HBR patients, PCI was more frequently performed in the anatomical setting of the left main and saphenous vein bypass grafts. New generation drug eluting stents were used in 93.4% of all patients with a lower frequency in patients at HBR. The use of potent P2Y12 inhibitors was less frequent in patients at HBR.



*ARC-HBR criteria*

Prevalence of ARC-HBR criteria is summarized in **Figure 1**. Age≥75 years (31.9%), anemia (26.4%), chronic kidney disease (CKD) (25.5%), oral anticoagulation (10.5%), previous intracranial hemorrhage or stroke (8.0%) were the leading ARC-HBR criteria in decreasing order. Prior spontaneous non-ICH bleeding (2.8%), thrombocytopenia (1.3%), NSAIDS (1.7%), and active malignancy (1.9%) were rarely observed. Major CKD, major anemia, and spontaneous non-ICH bleeding frequently overlapped with other criteria as illustrated in **Supplementary figure 1**. The ARC-HBR score had a C statistic of 0.69 (95% CI 0.66-0.71)

for BARC 3 or 5 bleeding and showed accurate calibration (**Supplementary figure 2**). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the ARC-HBR score ≥1 (i.e. equivalent to 1 major or 2 minor ARC-HBR criteria) for BARC 3 or 5 bleeding at 1 year were 68.5%, 61.7%, 6.4%, 98.1%, and 61.9%, respectively. As an explanatory analysis, we compared the diagnostic ability and C statistics among ARC-HBR score, PRECISE-DAPT score, and PARIS bleeding score in patients in whom all 3 scores were available (n=10551) (**Figure 2**). The ARC-HBR criteria had higher sensitivity compared with other bleeding risk scores at the cost of lower specificity.



*Clinical outcomes*

Clinical outcomes at 1-year are summarized in **Table 2**. Compared to patients without HBR, those at HBR had an increased risk of BARC 3 or 5 bleeding (6.4% vs. 1.9%, P<0.001) and device-oriented composite endpoints (DOCE) (12.5% vs. 6.1%, P<0.001) as well as other secondary endpoints including net adverse composite endpoints, all-cause death, cardiac death, myocardial infarction, target lesion revascularization, definite stent thrombosis, stroke, and each BARC component. Patients at HBR had an increased risk of BARC 3 or 5 bleeding after considering all-cause death as a competing risk (hazard ratio: 3.44; 95% confidence interval: 2.80 to 4.17; P<0.001). There was a gradual risk increase for BARC 3 or 5 bleeding (0, 0.5: 1.9%, 1: 4.6%, and ≥1.5: 7.6%, P <0.001) and DOCE (0, 0.5: 6.1%, 1: 10.6%, and ≥1.5: 13.9%,

P <0.001) as a function of the ARC-HBR score (**Figure 3**). The frequency of BARC 3 or 5 bleeding and DOCE for each ARC-HBR score were: 0: 1.6% and 5.6%, 0.5: 2.9% and 7.4%, 1: 4.6% and 10.6%, 1.5: 4.9% and 13.0%, 2: 8.5% and 13.2%, 2.5: 9.0% and 13.6%, ≥3: 10.9% and 17.9%, respectively (**Figure 4**). Each ARC-HBR criterion except for NSAIDS at discharge was associated with a BARC 3 or 5 bleeding risk of ≥4% (**Figure 5**), while the bleeding risk associated with ARC-HBR score 0.5 or 1 was dependent on the individual criteria of the score (**Table 3**).



*COX regression analysis*

The unadjusted and adjusted risks of individual components of the ARC-HBR criteria for BARC 3 or 5 and DOCE at 1 year are presented in **Table 4** and **Supplementary table 4**, respectively. Oral anticoagulant (OAC) or novel oral anticoagulant at discharge and prior spontaneous non-ICH bleeding emerged as independent predictors for BARC 3 or 5 bleeding at 1 year, while CKD and anemia were associated with both BARC 3 or 5 bleeding and DOCE.

## Discussion

The implementation of bleeding avoidance strategies is considered relevant as bleeding contributes substantially to adverse outcomes including mortality.[1,2] Guidelines support the use of bleeding risk scores (class IIb, level A) to predict bleeding and potentially tailor

antithrombotic therapies. However, these scores depend on the characteristics of patients included in the derivation cohort and are not necessarily applicable to routine clinical practice. The ARC-HBR criteria represent a new and pragmatic consensus-based approach to predict bleeding and our study aims to evaluate in detail the ARC-HBR criteria using an unselected PCI population consecutively enrolled at a large tertiary care center.

Patients at HBR according to the ARC-HBR criteria were frequent (≈40%). The criteria including age ≥75 years, CKD, anemia, oral anticoagulation, and previous ICH or stroke were frequently observed in the real-world PCI population in line with inclusion criteria applied in previous HBR studies,[7,9] while prior spontaneous non-ICH bleeding, thrombocytopenia, NSAIDS, and active malignancy were relatively rare.

Patients at HBR had a higher risk (6.4%) of bleeding at 1 year defined by BARC 3 or 5 exceeding the anticipated treshold of 4.0%. The rate of BARC 3 or 5 bleeding of 1.9% at 1 year in patients without HBR was comparable with results obtained from previous DAPT trials (i.e. <3.0%) with sytematic exclusion of HBR patients.[10] It is noteworthy that patients fullfilling one minor criterion carried a 2-fold higher bleeding risk as compared with patients without HBR (2.9% vs. 1.6%). Further studies should investigate whether "intermediate risk" patients (i.e. one minor criterion) and "truly low risk" (i.e. no criterion) should be treated equally in terms of DAPT intensity and duration.

Although the bleeding risk increased proportionally with increasing number of ARC-HBR criteria, importantly, the degree of risk and prognostic value varied considerably among the ARC-HBR criteria. In the ARC-HBR consensus document, a major criterion is defined as any criterion that, in isolation, confers a BARC 3 or 5 bleeding risk of ≥4% at 1 year and a minor criterion is defined as any criterion that, in isolation, confers increased bleeding risk with a BARC 3 or 5 bleeding rate of <4% at 1 year.[10] Although this analysis includes only a limited number of patients with each criterion being present in isolation, not all criteria met the expectation of predicting a BARC 3 or 5 bleeding risk ≥4% (Major) or <4% (Minor). Patients who fullfilled only "anticipated longterm use of oral anticoagulant" (major criterion) had a BARC 3 or 5 bleeding rate of 2.5%, while patients with "eGFR ≥30, <60 ml/min/1.73m$^2$" (minor criterion) had a bleeding risk of 4.8% at 1-year. Our data suggests that the bleeding risk associated with ARC-HBR score 0.5 or 1 was dependent on the individual criteria composing the score. Physicians should note that an individualized approach based on the applied criteria may be needed in patients with ARC-HBR score 0.5 or 1.

Consistent with previous analyses,[16] HBR patients did not only incur an increased risk of bleeding but also multiple ischemic events including cardiac death, myocardial infarction and stent thrombosis. HBR patients had more frequent risk factors correlating with atherosclerotic disease burden such as diabetes mellitus and previous revascularization, explaining in part the excess in ischemic events. The dillematic dual impact of certain clinical

characteristics such as renal failure was consistent with one of our previous analyses on the same cohort[16] as well as previous studies.[6,17] Although many operators are still reluctant to use newer generation DES in HBR patients, there was only a small difference between groups in this cohort (92.0% vs. 94.3%), which may not be applied as an explanation for an increased risk of ischemic events. Patients categorized as HBR may represent a more frail population, a characteristic that was not specifically assessd in the Bern PCI registry, i.e. a notion supported by a higher frequency in non-cardiac mortality (4.2% vs. 0.3%).

The ARC-HBR criteria categorized approximately 40% of an unselected PCI population as HBR, while fewer patients were identified as HBR by other bleeding risk scores. Specifically, 26.9% of patients fulfilled the PRECISE-DAPT score ≥25 and 14.5% fulfilled the PARIS bleeding score ≥8. Accordingly, the ARC-HBR criteria was more sensitive than others (ARC-HBR score ≥1: 63.8% vs. PRECISE-DAPT score ≥25: 53.1% vs. PARIS bleeding score ≥8: 31.9%) at the cost of specifity (62.7% vs. 71.3% vs. 86.5%). The c-statistics were comparable among the three bleeding prediction systems. In contrast to the consistently high negative predictive value, a limited positive predictive value represents a common limitation of clinical bleeding prediction tools, although an impact of a relatively low rate of bleeding events on positive predictive value needs to be considered. In light of a limited performance of bleeding prediction systems and the large overlap with ischemic events in HBR patients, it remains of

outmost importance to conduct RCTs investigating the impact of score-based treatment strategies.

To date, only one study attempted to validate the ARC-HBR criteria and suggested that patients at HBR had a higher bleeding rate and that each individual ARC-HBR criterion was associated with major bleeding risk >4% at 1 year.[18] However, the analysis did not include BARC bleeding as endpoints and was done in Asian (Japanese) population. In the present study, we confirmed consistent results with the BARC bleeding definition using the large PCI dataset of European population.



**Limitations**

First, the single-center design of this study may limit the generalizability of our findings. Second, 4 ARC-HBR criteria were not applicable and 3 needed to be substantially modified due to the data availability in the registry, which might hinder a complete review of criteria and precise estimates of the bleeding risk for each HBR criterion in isolation as well as potential cumulative effects, although missing criteria in the present study appear to be rare. Lastly, DAPT duration and intensity can not be considered due to the nature of the observational study design. The results need to be interpreted against the background of a routine 12-month DAPT duration determined by operator's discretion in most patients, while bleeding risk associated

with oral anticoagulation might be underestimated due to shortened duration of DAPT in patients with triple therapy (i.e. DAPT and OACs).

**Conclusions**

Patients at HBR defined by the ARC-HBR criteria were as frequent as 40% and had not only a higher risk of BARC 3 or 5 bleeding but also ischemic events. The bleeding risk was proportional to the risk score and related to its individual components. The low positive predictive value of the ARC-HBR criteria for BARC 3 or 5 bleeding remains a notable limitation.

**Impact on daily practice**

The application of the ARC-HBR criteria to identify BARC 3 or 5 bleeding at 1 year in patients undergoing PCI carries a high negative but low positive predictive value. The bleeding risk was related to its individual components. Physicians should note that an individualized approach may be needed based on the applied criteria.

**Figure Legends**

**Figure 1.** Distribution of the ARC-HBR criteria

DAPT = dual antiplatelet therapy, ICH = intracranial hemorrhage, NOAC = novel oral anticoagulant, OAC = oral anticoagulant, PCI = percutaneous coronary intervention.

**Figure 2.** ROC curves and diagnostic ability of bleeding prediction systems for 1-year BARC 3 or 5 bleeding

BARC = bleeding academic research consortium, CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, Sn = sensitivity, Sp = specificity.

**Figure 3.** Kaplan-Meier cumulative event curves for BARC 3 or 5 bleeding and DOCE at 1 year stratified by the ARC-HBR score

BARC = bleeding academic research consortium, DOCE = device-oriented composite endpoints, PCI = percutaneous coronary intervention.

**Figure 4.** Event rates according to the ARC-HBR score

BARC = bleeding academic research consortium, DOCE = device-oriented composite endpoints.

**Figure 5.** Event rates at 1 year according to ARC-HBR criteria

BARC = bleeding academic research consortium, DAPT = dual antiplatelet therapy, DOCE = device-oriented composite endpoints, ICH = intracranial hemorrhage, NOAC = novel oral anticoagulant, OAC = oral anticoagulant, PCI = percutaneous coronary intervention.

**Table 1.** Patient characteristics

| | HBR (n=4781) | Non-HBR (n=7340) | P value |
|---|---|---|---|
| Age (years) | 75.5±10.0 | 62.8±10.4 | <0.001 |
| Age ≥75 years | 3026 (63.3%) | 843 (11.5%) | <0.001 |
| Female | 1644 (34.4%) | 1505 (20.5%) | <0.001 |
| Body mass index (kg/m$^2$) | 26.7±4.9 | 27.8±4.5 | <0.001 |
| Current smoker | 765 (16.0%) | 2502 (34.1%) | <0.001 |
| Hypertension | 3780 (79.1%) | 4607 (62.8%) | <0.001 |
| Diabetes mellitus | 1347 (28.2%) | 1430 (19.5%) | <0.001 |
| Dyslipidemia | 3125 (65.4%) | 4700 (64.0%) | 0.060 |
| Family history of coronary artery disease | 972 (20.3%) | 2199 (30.0%) | <0.001 |
| Previous myocardial infarction | 932 (19.5%) | 1028 (14.0%) | <0.001 |
| Previous PCI | 1127 (23.6%) | 1418 (19.3%) | <0.001 |
| Previous CABG | 677 (14.2%) | 518 (7.1%) | <0.001 |
| Peripheral artery disease | 609 (12.7%) | 361 (4.9%) | <0.001 |
| Prior spontaneous non-ICH bleeding requiring hospitalization or transfusion | 338 (7.1%) | 0 (0%) | <0.001 |

| | | | |
|---|---|---|---|
| Active malignancy (excluding nonmelanoma skin cancer) within past 12 months | 234 (4.9%) | 0 (0%) | <0.001 |
| Previous ICH or previous stroke | 146 (3.2%) | 0 (0%) | <0.001 |
| Any ischemic stroke at any time not meeting the major criterion | 965 (20.2%) | 0 (0%) | <0.001 |
| Left ventricular ejection fraction (%) | 50.6±14.9 | 54.2±12.3 | <0.001 |
| eGFR | 62.4±30.1 | 101±32.3 | <0.001 |
| eGFR ≥30, <60 ml/min/1.73m$^2$ | 2344 (49.0%) | 314 (4.3%) | <0.001 |
| eGFR <30 ml/min/1.73m$^2$ | 434 (9.1%) | 0 (0%) | <0.001 |
| Hemoglobin (g/dL) | 12.5±2.0 | 14.3±1.3 | <0.001 |
| Hemoglobin 11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females) | 1362 (28.5%) | 739 (10.1%) | <0.001 |
| Hemoglobin ≤11.0 g/dL | 1095 (22.9%) | 0 (0%) | <0.001 |
| Thrombocytes (×10$^9$/L) | 226±84.8 | 228±63.1 | <0.001 |
| Thrombocytes <100 ×10$^9$/L | 155 (3.2%) | 0 (0%) | <0.001 |
| Clinical indication for PCI | | | |
| Chronic coronary syndrome | 2356 (49.3%) | 2995 (40.8%) | <0.001 |
| Acute coronary syndrome | | | <0.001 |

| | | | |
|---|---|---|---|
| Unstable angina | 209 (4.4%) | 380 (5.2%) | |
| Non-ST elevation myocardial infarction | 1286 (26.9%) | 1731 (23.6%) | |
| ST elevation myocardial infarction | 930 (19.5%) | 2234 (30.4%) | |
| PRECISE-DAPT score | 27.6 (11.4) | 13.7 (7.4) | <0.001 |
| Medication | | | |
| Aspirin | 4466 (93.4%) | 7187 (97.9%) | <0.001 |
| Clopidogrel | 3449 (72.1%) | 3417 (46.6%) | <0.001 |
| Potent P2Y12 (prasugrel or ticagrelor) | 1180 (24.7%) | 3857 (52.5%) | <0.001 |
| Any DAPT | 4413 (92.3%) | 7155 (97.5%) | <0.001 |
| OAC or NOAC | 1271 (26.6%) | 0 (0%) | <0.001 |
| Any DAPT and OAC/NOAC | 1079 (22.6%) | 0 (0%) | <0.001 |
| NSAIDS at discharge | 117 (2.5%) | 86 (1.2%) | <0.001 |

Values are n (%) or mean±SD.

CABG = coronary artery bypass graft, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, HBR = high bleeding risk, ICH = intracranial hemorrhage, PCI = percutaneous coronary intervention NOAC = novel oral anticoagulant, OAC = oral anticoagulant.

**Table 2.** Event rate at 1 year

| | HBR (n=4781) | Non-HBR (n=7340) | P value |
|---|---|---|---|
| **Primary endpoint** | | | |
| BARC 3 or 5 bleeding | 304 (6.4%) | 140 (1.9%) | <0.001 |
| **Secondary endpoints** | | | |
| DOCE (cardiac death, TV-MI, TLR) | 600 (12.5%) | 446 (6.1%) | <0.001 |
| NACE (cardiac death, TV-MI, TLR, BARC 3 or 5 bleeding) | 923 (19.3%) | 642 (8.8%) | <0.001 |
| All-cause death | 529 (11.1%) | 120 (1.6%) | <0.001 |
| Cardiac death | 330 (6.9%) | 92 (1.3%) | <0.001 |
| Myocardial infarction | 288 (6.0%) | 270 (3.7%) | <0.001 |
| Target vessel myocardial infarction | 209 (4.4%) | 210 (2.9%) | <0.001 |
| Spontaneous myocardial infarction | 156 (3.3%) | 126 (1.7%) | <0.001 |
| Any revascularization | 339 (7.1%) | 522 (7.1%) | 0.497 |
| Target lesion revascularization | 191 (4.0%) | 228 (3.1%) | 0.002 |
| Target vessel revascularization | 247 (5.2%) | 365 (5.0%) | 0.272 |
| Non-target vessel revascularization | 148 (3.1%) | 272 (3.7%) | 0.209 |
| Stent thrombosis (definite) | 68 (1.4%) | 67 (0.9%) | 0.007 |

| | | | |
|---|---|---|---|
| Acute (≤24 hours) | 27 (0.6%) | 29 (0.4%) | 0.181 |
| Subacute (>24 hours to 30 days) | 20 (0.4%) | 25 (0.3%) | 0.460 |
| Late (>30 days to 1 year) | 21 (0.4%) | 13 (0.2%) | 0.006 |
| Stroke | 105 (2.2%) | 50 (0.7%) | <0.001 |
| Any bleeding | 413 (8.6%) | 229 (3.1%) | <0.001 |
| BARC (2, 3, 5) bleeding | 409 (8.6%) | 219 (3.0%) | <0.001 |
| BARC (2) bleeding | 138 (3.0%) | 93 (1.3%) | <0.001 |
| BARC (3) bleeding | 285 (6.2%) | 135 (1.8%) | <0.001 |
| BARC (4) bleeding | 6 (0.1%) | 12 (0.2%) | 0.646 |
| BARC (5) bleeding | 19 (0.4%) | 5 (0.1%) | <0.001 |

Values are n (%).

BARC = bleeding academic research consortium, DOCE = device-oriented composite endpoints, NACE = net adverse composite endpoints, TLR = target lesion revascularization, TV-MI = target vessel myocardial infarction.

**Table 3.** BARC 3 or 5 bleeding rates in patients with the ARC-HBR score 1 and 0.5.

| Criteria | BARC 3 or 5 bleeding |
|---|---|
| **ARC-HBR score = 1 (n=1910)** | |
| **Major criteria** | |
| OAC or NOAC at discharge (n=284) | 7 (2.5%) |
| CKD (Major) (n=13) | 2 (15.4%) |
| Anemia (Major) (n=151) | 12 (8.0%) |
| Spontaneous non-ICH bleeding (n=52) | 1 (1.9%) |
| Thrombocytes <100 x$10^9$/l (n=16) | 3 (18.8%) |
| Active malignancy within past 12 months (n=40) | 3 (7.5%) |
| ICH or stroke (n=243) | 7 (2.9%) |
| **Combination of minor criteria** | |
| Age ≥75 years + CKD (Minor) (n=750) | 38 (5.1%) |
| Age ≥75 years + Anemia (Minor) (n=213) | 8 (3.8%) |
| Age ≥75 years + NSAIDS at discharge (n=15) | 0 (0%) |
| CKD (Minor) + Anemia (Minor) (n=106) | 6 (5.7%) |
| CKD (Minor) + NSAIDS at discharge (n=6) | 0 (0%) |
| Anemia (Minor) + NSAIDS at discharge (n=21) | 0 (0%) |

| | |
|---|---|
| **ARC-HBR score = 0.5 (n=1982)** | |
| **Minor criteria** | |
| Age ≥75 years (n=843) | 27 (3.2%) |
| CKD (Minor) (n=314) | 15 (4.8%) |
| Anemia (Minor) (n=739) | 15 (2.0%) |
| NSAIDS at discharge (n=86) | 0 (0%) |

Values are n (%).

BARC = bleeding academic research consortium, CKD = chronic kidney disease, DAPT = dual antiplatelet therapy, DOCE = device-oriented composite endpoints, ICH = intracranial hemorrhage, NOAC = novel oral anticoagulant, OAC = oral anticoagulant, PCI = percutaneous coronary intervention.

**Table 4.** Cox analysis for BARC 3 or 5 bleeding

| | Univariate | | Multivariate model 1 | | Multivariate model 2 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| **Age ≥75 years** | 2.15 (1.79-2.59) | <0.001 | 1.82 (1.47-2.26) | <0.001 | 1.20 (0.95-1.53) | 0.125 |
| **OAC or NOAC at discharge** | 2.06 (1.62-2.61) | <0.001 | 2.14 (1.65-2.77) | <0.001 | 1.87 (1.44-2.43) | <0.001 |
| **Chronic kidney disease** | | | | | | |
| eGFR ≥60 ml/min/1.73m$^2$ | reference | | reference | | reference | |
| eGFR ≥30, <60 ml/min/1.73m$^2$ | 2.80 (2.29-3.40) | <0.001 | 2.52 (2.01-3.17) | <0.001 | 1.82 (1.41-2.36) | <0.001 |
| eGFR <30 ml/min/1.73m$^2$ | 4.47 (3.22-6.19) | <0.001 | 3.88 (2.70-5.59) | <0.001 | 1.98 (1.33-2.95) | 0.001 |
| **Anemia** | | | | | | |
| ≥13.0 g/dL (males) or 12.0 g/dL (females) | reference | | reference | | reference | |
| 11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females) | 1.69 (1.33-2.16) | <0.001 | 1.58 (1.23-2.04) | <0.001 | 1.32 (1.02-1.71) | 0.036 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≤11.0 g/dL | 4.60 (3.69-5.74) | <0.001 | 3.89 (3.04-4.97) | <0.001 | 2.64 (2.01-3.47) | <0.001 |
| **Spontaneous non-ICH bleeding** | 3.33 (2.38-4.66) | <0.001 | 2.94 (2.07-4.19) | <0.001 | 1.89 (1.31-2.73) | 0.001 |
| **Thrombocytes <100 x$10^9$/l** | 3.30 (2.00-5.43) | <0.001 | 2.62 (1.47-4.66) | 0.001 | 1.53 (0.85-2.75) | 0.154 |
| **NSAIDS at discharge** | 0.53 (0.20-1.41) | 0.202 | 0.42 (0.14-1.31) | 0.136 | 0.47 (0.15-1.47) | 0.197 |
| **Active malignancy within past 12 months** | 2.31 (1.44-3.70) | 0.001 | 2.20 (1.35-3.59) | 0.001 | 1.49 (0.90-2.42) | 0.127 |
| **ICH or stroke** | 1.32 (0.97-1.80) | 0.074 | 1.16 (0.83-1.61) | 0.382 | 0.96 (0.69-1.33) | 0.785 |

Of the study patients, 96.4% (11689/12121) were entered into the multivariable model for BARC 3 or 5 bleeding.

In the model 1, each criterion was adjusted by following variables. In the model 2, each criterion was adjusted by following variables and all components of the ARC-HBR criteria. Variables: female, body mass index, current smoker, hypertension, peripheral artery disease, acute coronary syndrome, potent P2Y12 at discharge.

BARC = bleeding academic research consortium, CI = confidence interval, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, NOAC = novel oral anticoagulant, HR = hazard ratio, ICH = intracranial hemorrhage, OAC = oral anticoagulant, PCI = percutaneous coronary intervention.

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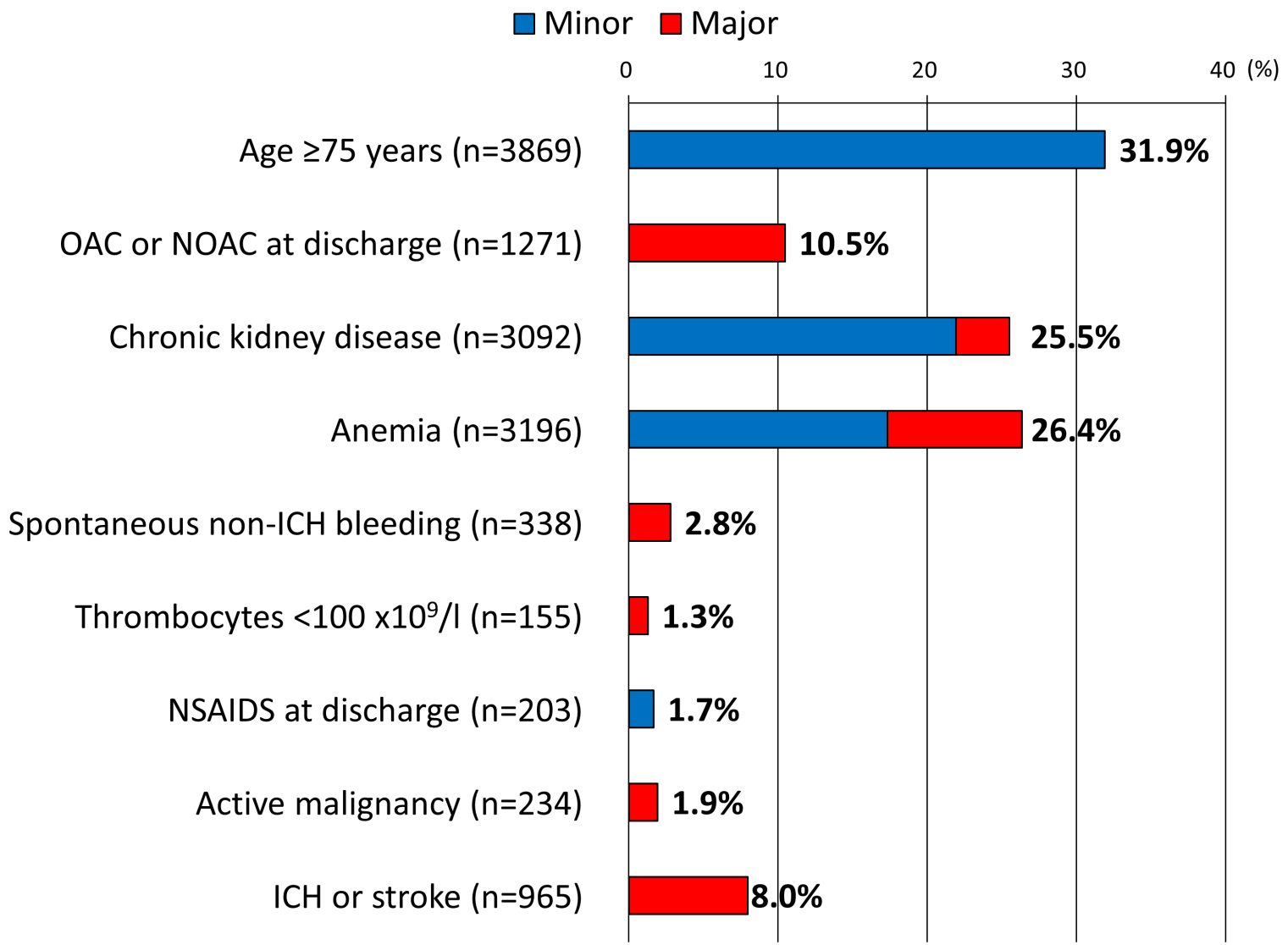

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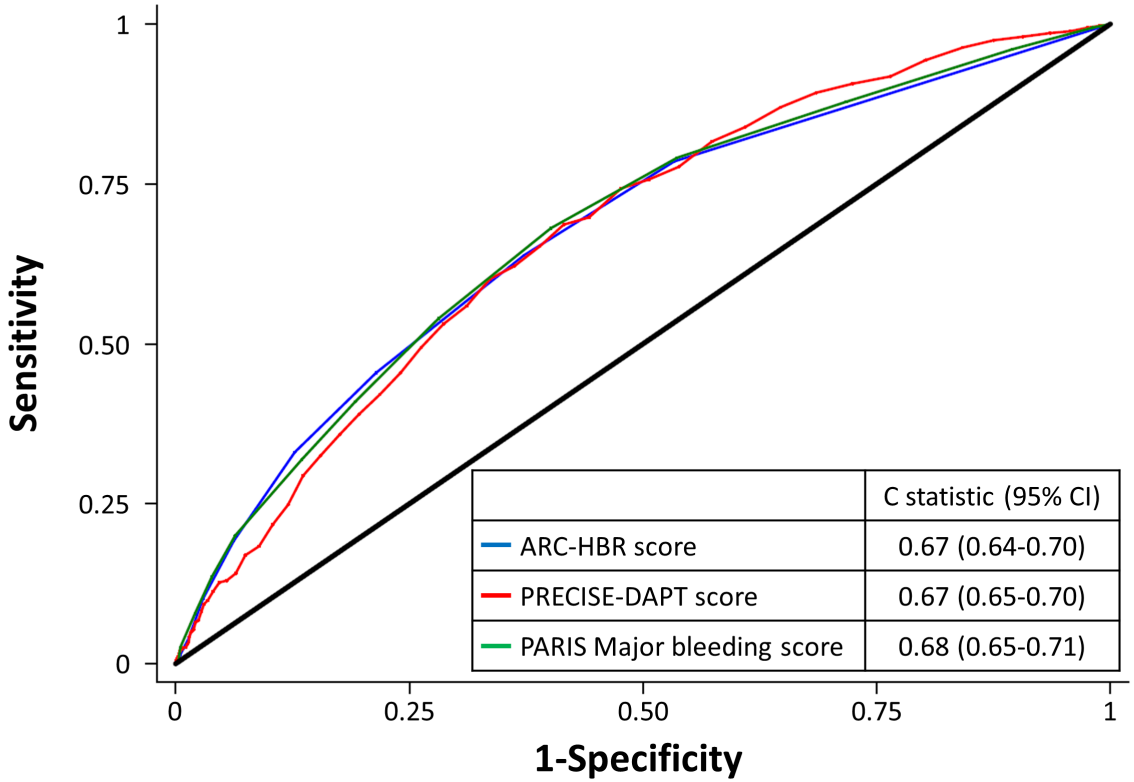
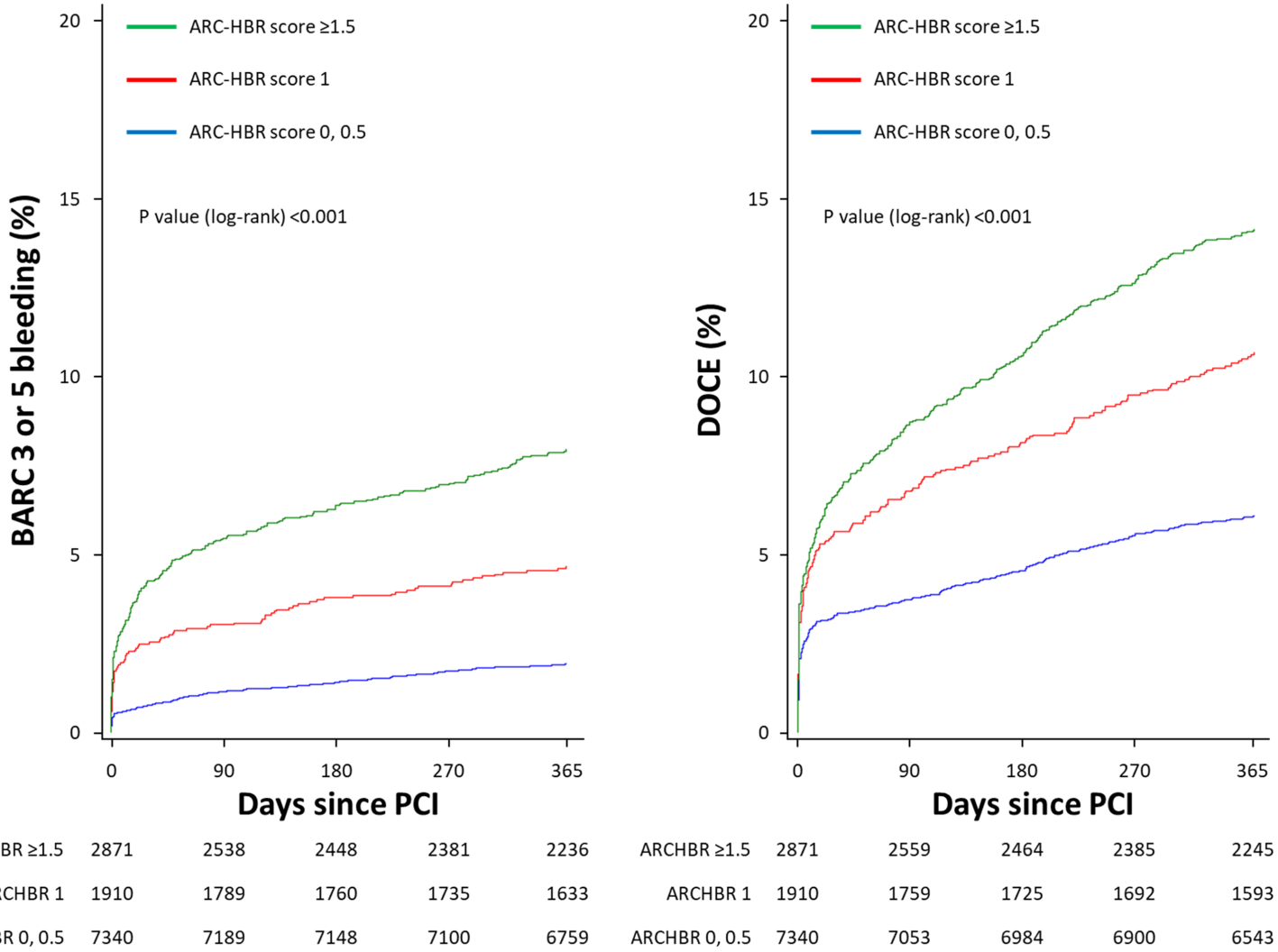
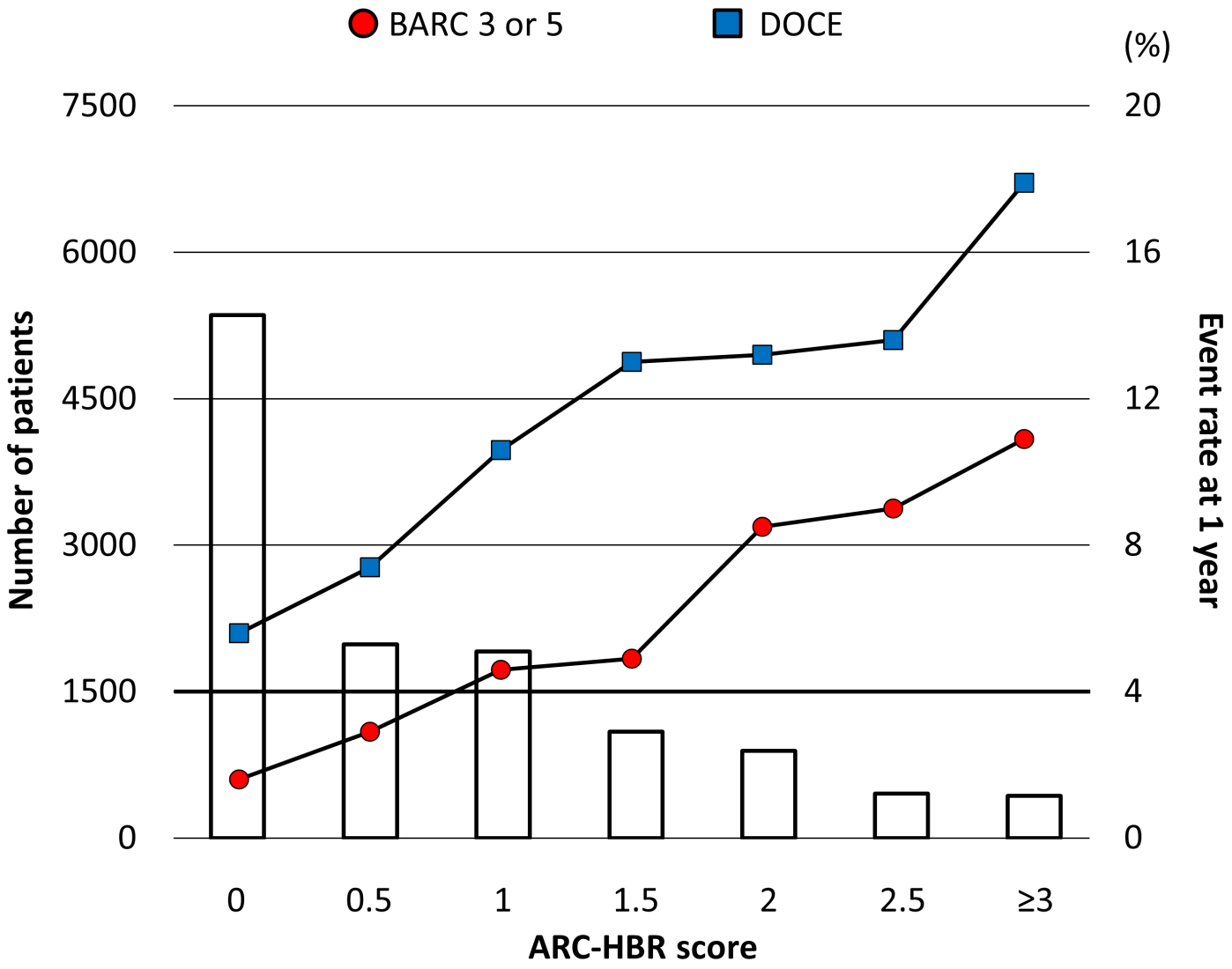


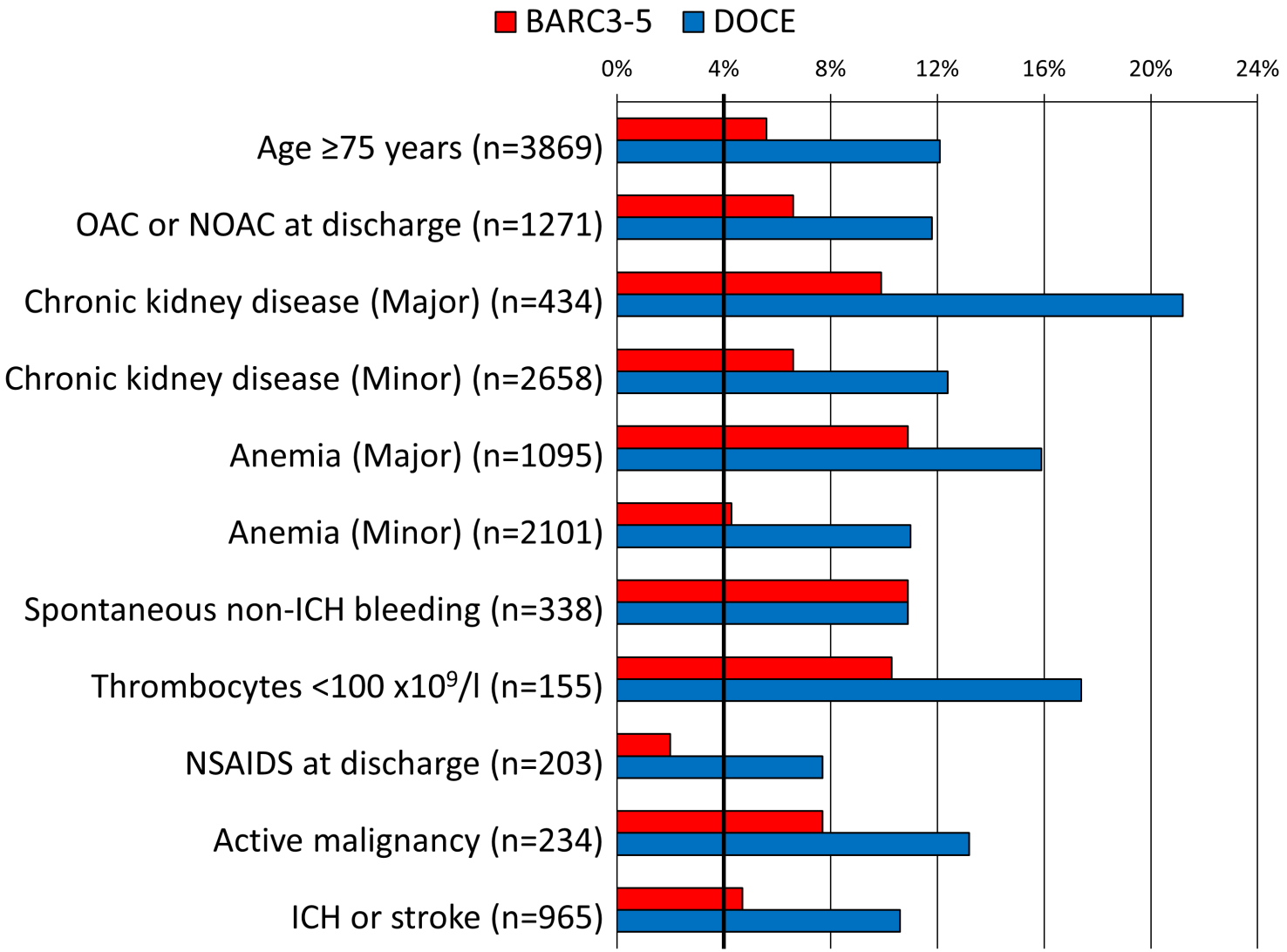

| | Sn (%) | Sp (%) | PPV (%) | NPV (%) | Accuracy (%) |
|---|---|---|---|---|---|
| ARC-HBR score (≥1) | 63.8 | 62.7 | 5.6 | 98.0 | 62.8 |
| PRECISE-DAPT score (≥25) | 53.1 | 71.3 | 6.0 | 97.8 | 70.7 |
| PARIS Major bleeding score (≥8) | 31.9 | 86.5 | 7.6 | 97.3 | 84.7 |




| | | | | | |
|---|---|---|---|---|---|
| ARCHBR ≥1.5 | 2871 | 2538 | 2448 | 2381 | 2236 |
| ARCHBR 1 | 1910 | 1789 | 1760 | 1735 | 1633 |
| ARCHBR 0, 0.5 | 7340 | 7189 | 7148 | 7100 | 6759 |

| | | | | | |
|---|---|---|---|---|---|
| ARCHBR ≥1.5 | 2871 | 2559 | 2464 | 2385 | 2245 |
| ARCHBR 1 | 1910 | 1759 | 1725 | 1692 | 1593 |
| ARCHBR 0, 0.5 | 7340 | 7053 | 6984 | 6900 | 6543 |





**Online Appendix**

# Validation of Bleeding Risk Criteria (ARC-HBR) in Patients Undergoing Percutaneous Coronary Intervention

**Ueki et al.**

**Clinical endpoints and definitions**

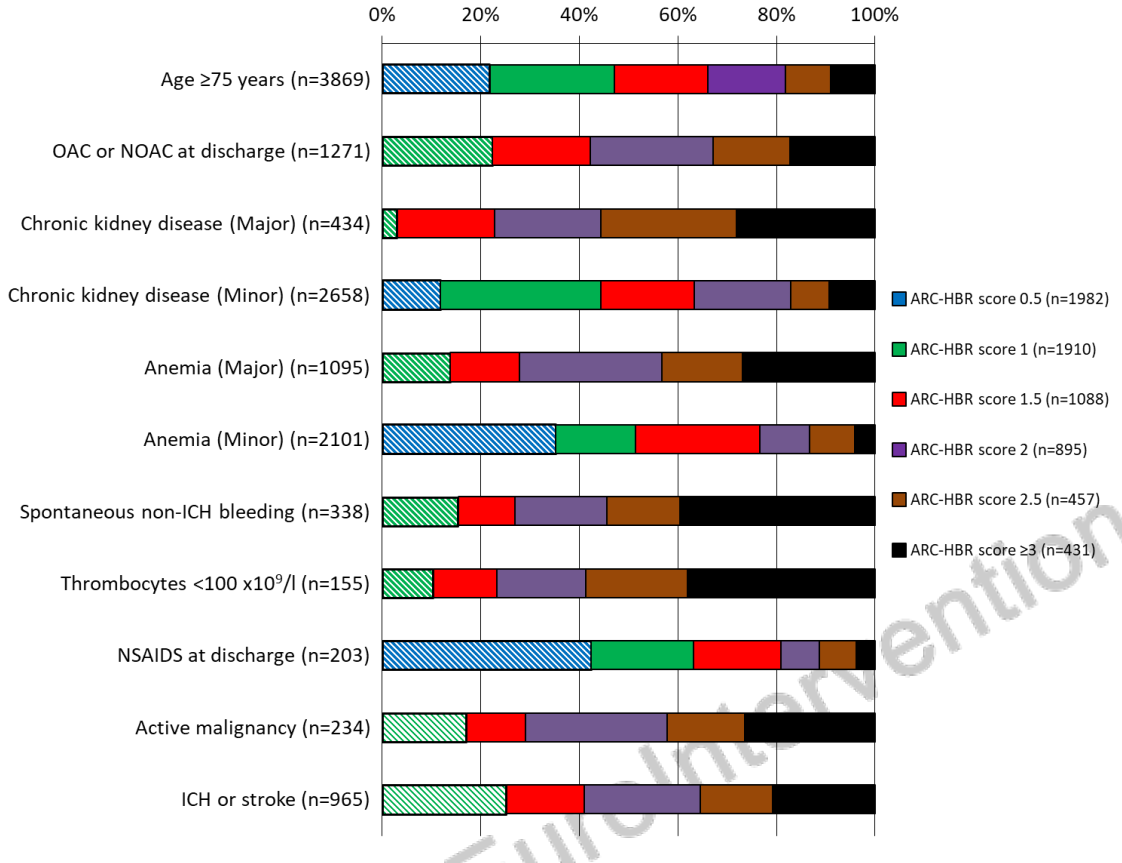
A clinical event committee consisting of 2 cardiologists (and a third referee in case of disagreement) adjudicated all events against original source documents. Secondary endpoints were: the device oriented composite endpoints (DOCE), defined as a composite of cardiac death, target-vessel (TV) MI, and target lesion revascularization (TLR); the net adverse composite endpoints (NACE), defined as cardiac death, TV-MI, TLR, and BARC 3 or 5; all-cause death; cardiac death; any MI; TV-MI; any repeat revascularization; TLR; target vessel revascularization (TVR); non-TVR; definite stent thrombosis (ST); stroke; any bleeding; and BARC 2, 3, or 5. Cardiac death was defined as any death caused by an immediate cardiac cause, procedure-related mortality, and death of unknown cause. MI was defined according to the modified historical definition. ST was classified according to the Academic Research Consortium criteria. Stroke was defined as rapid development of clinical signs of focal or global disturbance of cerebral function lasting >24 hours with imaging evidence of acute, clinically relevant ischemic brain lesion. Ischemic cerebral infarctions with conversion to hemorrhage were categorized as stroke. Intracerebral hemorrhages were defined as rapid development of clinical signs of focal or global disturbance of cerebral function and imaging evidence of clinically relevant intracerebral bleeding. Spontaneous bleeding was defined as a history of previous clinically significant bleeding requiring medical attention.[5] On-going

treatment of cancer was defined as planning for surgery or currently undergoing oncological systemic therapy (i.e. chemo-, hormone, and biological therapy) and/or radiation at index PCI.

**Patient follow-up**

Patients were systematically and prospectively followed throughout 1 year to assess death, myocardial infarction (MI), cerebrovascular accidents, revascularization, stent thrombosis (ST), bleeding complications, re-hospitalization and medical treatment. A health questionnaire was sent to all living patients with questions on re-hospitalization and adverse events, followed by telephone contact in case of missing response. General practitioners and referring cardiologists were contacted as necessary for additional information. For patients treated for adverse events at other medical institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed.

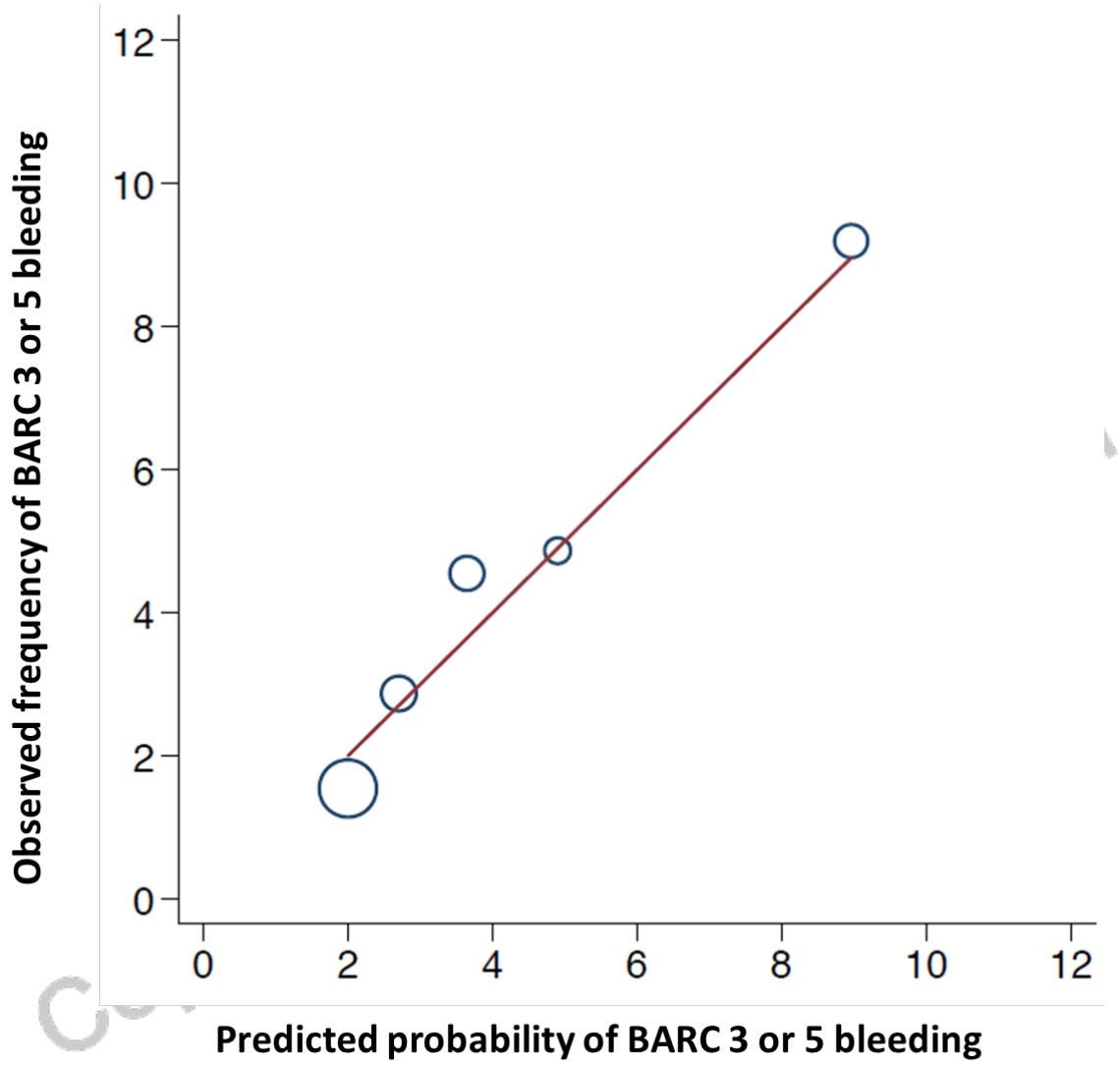
**Supplementary Figure 1.** Overlap of ARC-HBR criteria




Diagonal line depicts patients fulfilling each criterion in isolation.

DAPT = dual antiplatelet therapy, ICH = intracranial hemorrhage, NOAC = novel oral anticoagulant, OAC = oral anticoagulant, PCI = percutaneous coronary intervention.

**Supplementary figure 2.** Calibration plot of the ARC-HBR score for BARC 3 or 5 bleeding at 1 year




Calibration was examined by dividing patients in quintiles according to their predicted risk. The mean predicted risk per quintile group was subsequently plotted against the observed risk per quintile group. Size of the circle depicts the sample size of each quintile group.

BARC = bleeding academic research consortium.

**Supplementary table 1.** Comparison of definitions between the ARC-HBR and the present study

| ARC-HBR criteria | Present study | Category | Comments |
|---|---|---|---|
| Age ≥75 | Age ≥75 years | Minor | Identical |
| Anticipated use of long-term oral anticoagulation | Oral anticoagulant or novel oral anticoagulant at discharge | Major | Modified |
| Severe or end-stage CKD (eGFR <30 mL/min) | eGFR <30ml/min or hemodialysis | Major | Modified |
| Moderate CKD (eGFR 30–59 mL/ min) | eGFR ≥30, <60 ml/min | Minor | Identical |
| Hemoglobin <11 g/dL | Hemoglobin at index PCI <11g/dL | Major | Identical |
| Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women | Hemoglobin at index PCI 11–12.9 g/dL for men and 11–11.9 g/dL for women | Minor | Identical |
| Spontaneous non-intracranial bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent | Spontaneous non-intracranial bleeding requiring hospitalization or transfusion | Major | Modified |

| | | | |
|---|---|---|---|
| Spontaneous non-intracranial bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion | | Minor | Not available |
| Moderate or severe baseline thrombocytopenia (platelet count <100 $\times 10^9$/L) | Thrombocytes at index PCI <100 $\times 10^9$/L | Major | Identical |
| Chronic bleeding diathesis | | Major | Not available |
| Liver cirrhosis with portal hypertension | | Major | Not available |
| Long-term use of oral NSAIDs or steroids | NSAIDS at discharge | Minor | Modified |
| Active malignancy (excluding nonmelanoma skin cancer) within the past 12 mo | Cancer history within 1 year prior to index PCI or on-going treatment, excluding non-melanoma skin cancer | Major | Identical |
| Previous spontaneous ICH (at any time)<br>Previous traumatic ICH within the past 12 mo<br>Presence of a bAVM | Previous stroke or previous ICH | Major | Modified |

| | | | |
|---|---|---|---|
| Moderate or severe ischemic stroke within the past 6 mo | | | |
| Any ischemic stroke at any time not meeting the major criterion | | Minor | Not available |
| Planned nondeferrable noncardiac major surgery on DAPT | | Major | Not available |
| Recent major surgery or major trauma within 30 d before PCI | | Major | Not available |

bAVM = brain arteriovenous malformation, CKD = chronic kidney disease, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, ICH = intracranial hemorrhage, PCI = percutaneous coronary intervention.

**Supplementary table 2.** Procedural characteristics

| | HBR (n=4781) | Non-HBR (n=7340) | P value |
|---|---|---|---|
| Target lesion coronary artery | | | |
| Left main artery | 328 (6.9%) | 203 (2.8%) | <0.001 |
| Left anterior descending artery | 2440 (51.0%) | 3957 (53.9%) | 0.002 |
| Left circumflex artery | 1545 (32.3%) | 2377 (32.4%) | 0.940 |
| Right coronary artery | 1777 (37.2%) | 2697 (36.7%) | 0.640 |
| Bypass graft | 234 (4.9%) | 165 (2.3%) | <0.001 |
| Number of lesions | | | 0.160 |
| 1 | 2596 (54.3%) | 4095 (55.8%) | |
| 2 | 1409 (29.5%) | 2136 (29.1%) | |
| ≥3 | 776 (16.2%) | 1109 (15.1%) | |
| Lesion type | | | |
| In-stent restenosis | 238 (5.0%) | 354 (4.8%) | 0.700 |
| Thrombus | 630 (13.2%) | 1807 (24.6%) | <0.001 |
| Chronic total occlusion | 161 (3.4%) | 300 (4.1%) | 0.041 |
| Number of stents | | | 0.160 |

| | | | |
|---|---|---|---|
| 1 | 1995 (41.7%) | 3045 (41.5%) | |
| 2 | 1385 (29.0%) | 2235 (30.4%) | |
| ≥3 | 1401 (29.3%) | 2060 (28.1%) | |
| Stent type | | | <0.001 |
| New generation DES | 4397 (92.0%) | 6918 (94.3%) | |
| 1st generation DES | 25 (0.5%) | 34 (0.5%) | |
| Bare metal stent | 359 (7.5%) | 388 (5.3%) | |
| Total device length (mm) | 42.5±28.6 | 41.6±27.4 | 0.060 |
| Mean stent diameter (mm) | 3.0±0.6 | 3.0±0.4 | 0.250 |
| Bifurcation with two stents implanted | 283 (5.9%) | 437 (6.0%) | 0.940 |

Values are n (%) or mean±SD.

DES = drug eluting stents, HBR = high bleeding risk.

**Supplementary table 3.** Medication at 1 year

| | HBR (n=4781) | Non-HBR (n=7340) | P value |
|---|---|---|---|
| Aspirin | 3282 (68.6%) | 6294 (85.7%) | <0.001 |
| Clopidogrel | 1084 (22.7%) | 1456 (19.8%) | <0.001 |
| Potent P2Y12 (prasugrel or ticagrelor) | 425 (8.9%) | 1946 (26.5%) | <0.001 |
| Any DAPT | 1233 (25.8%) | 3086 (42.0%) | <0.001 |
| OAC or NOAC | 1061 (22.2%) | 219 (3.0%) | <0.001 |
| Any DAPT and OAC/NOAC | 52 (1.1%) | 8 (0.1%) | <0.001 |

Values are n (%).

DAPT = dual antiplatelet therapy, HBR = high bleeding risk, NOAC = novel oral anticoagulant, OAC = oral anticoagulant.

**Supplementary table 4.** Cox analysis for DOCE

| | Univariate | | Multivariate model 1 | | Multivariate model 2 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| **Age ≥75 years** | 1.79 (1.58-2.02) | <0.001 | 1.48 (1.27-1.72) | <0.001 | 1.23 (1.03-1.46) | 0.020 |
| **OAC or NOAC at discharge** | 1.46 (1.23-1.73) | <0.001 | 1.06 (0.84-1.33) | 0.626 | 1.06 (0.85-1.33) | 0.602 |
| **Chronic kidney disease** | | | | | | |
| eGFR ≥60 ml/min/1.73m$^2$ | reference | | reference | | reference | |
| eGFR ≥30, <60 ml/min/1.73m$^2$ | 1.85 (1.62-2.12) | <0.001 | 1.33 (1.11-1.60) | 0.002 | 1.32 (1.10-1.59) | 0.003 |
| eGFR <30 ml/min/1.73m$^2$ | 3.39 (2.72-4.22) | <0.001 | 2.30 (1.69-3.14) | <0.001 | 2.06 (1.50-2.84) | <0.001 |
| **Anemia** | | | | | | |
| ≥13.0 g/dL (males) or 12.0 g/dL (females) | reference | | reference | | reference | |
| 11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females) | 1.57 (1.35-1.82) | <0.001 | 1.37 (1.15-1.63) | <0.001 | 1.32 (1.10-1.57) | 0.002 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≤11.0 g/dL | 2.38 (2.01-2.82) | <0.001 | 1.73 (1.39-2.15) | <0.001 | 1.57 (1.25-1.99) | <0.001 |
| **Spontaneous non-ICH bleeding** | 1.30 (0.93-1.80) | 0.121 | 0.76 (0.48-1.21) | 0.246 | 0.63 (0.40-1.00) | 0.052 |
| **Thrombocytes <100 x$10^9$/l** | 2.25 (1.53-3.29) | <0.001 | 1.60 (0.97-2.63) | 0.065 | 1.29 (0.78-2.14) | 0.320 |
| **NSAIDS at discharge** | 0.80 (0.47-1.35) | 0.396 | 0.74 (0.40-1.38) | 0.342 | 0.74 (0.40-1.38) | 0.345 |
| **Active malignancy within past 12 months** | 1.65 (1.15-2.36) | 0.006 | 1.49 (0.99-2.25) | 0.054 | 1.33 (0.88-2.02) | 0.174 |
| **ICH or stroke** | 1.26 (1.03-1.55) | 0.026 | 0.91 (0.70-1.18) | 0.480 | 0.90 (0.70-1.17) | 0.451 |

Of the study patients, 89.6% (10856/12121) were entered into the multivariable model for DOCE.

In the model 1, each criterion was adjusted by following variables. In the model 2, each criterion was adjusted by following variables and all components of the ARC-HBR criteria. Variables: age, female, current smoker, hypertension, peripheral artery disease, previous myocardial infarction, previous revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), left ventricular ejection fraction, stent type (bare-metal stent, first-generation drug-eluting stent.

BARC = bleeding academic research consortium, CI = confidence interval, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, NOAC = novel oral anticoagulant, HR = hazard ratio, ICH = intracranial hemorrhage, OAC = oral anticoagulant, PCI = percutaneous coronary intervention.